REMARKS

Reconsideration and allowance of the present application based on the following remarks are respectfully requested.

Upon entry of the above amendments, claims 15-25 will be pending. The new claims are all based on the original claims and do not introduce new matter, merely, more clearly defining the subject matter which Applicants regard as their invention using acceptable claim formatting for U.S. patent practice.

It is specifically noted, however, that the pH ranges in claims 15 and 16 are reversed from claims 1 and 2, since, in fact, the narrower range in the main claim is broader than the wider range in the dependent claim.

The amendments to the specification address the objection regarding the use of trademarks and correct other minor typographical errors. The heading "Brief Description of the Drawings" is added as requested in the Action. No new matter is added.

A new Information Disclosure Statement is being filed concurrently herewith in order to submit and have made of record, the documents mentioned in the specification. In addition, a partial English translation of JP 05 155776 is provided.

Regarding the objection to the oath or declaration, it is pointed out that GB, i.e., Great Britain, is identified in the address line for each of Mr. Roberts and Mr. Webb and, in addition, United Kingdom is included in the space for Residence, but only as a continuation of the Full Post Office Address, the residence being the same in each instance. Accordingly, it is believed that the Declaration is acceptable. However, should still further clarification be necessary, please advise and a new Declaration will be obtained. Nevertheless, acceptance of the Declaration on file is respectfully requested.

The objection to Figure 1 as containing only 7 of 8 sets of plotted data is respectfully traversed.

As explained on page 11, lines 14-16, "The Ca:Fe 3:1 compound (3) bound almost 100% of the phosphate independently of pH. <u>There was no difference between the aged and unaged compounds.</u>" (Emphasis added.) In other words, the line for "□ Ca:Fe 3:1 unaged" is present in Fig. 1, however, masked underneath the data points for "■ Ca:Fe 3:1 aged." Therefore, withdrawal of the objection to the drawings is requested. Nevertheless, if the objection is maintained, Applicants will consider cancelling the reference to "Ca:Fe 3:1 unaged" from Fig. 1.

The objections to claims 6, 7, 11 and 13, are obviated in the newly presented claims.

Regarding the 35 USC 112, second paragraph rejection of claims 1-14, in view of the phrase "phosphate binding capacity of at least 30% by weight of the total weight of the phosphate present" the new claims now specifically incorporate by reference, the test methods 1, 2, or 3, as described in the specification, (page 10). Accordingly, this basis for rejection is respectfully traversed.

The rejection as applied to former claims 6-10 is traversed as applied to the new claims 20 and 21. These claims are directed to the method for treating hyperphosphatameia by administering compounds according to the invention.

New claims 22-25 replace claims 11-14 and clarify that the metal sulphate is the solid material.

Accordingly, all of the rejections under 35 USC 112 are respectfully traversed and/or avoided.

As presently advised, all of the named inventors contributed to the subject matter of at least one pending claim.

Claims 1-14 are rejected as being obvious, within the meaning of 35 USC 103(a), over JP 5-155,776 in view of German Patent 34 02 878 to Dietl. This rejection is respectfully traversed for the following reasons.

For the convenience of the Examiner, a partial English language translation of JP 5-155,776 (JP-776) is provided.

As will be appreciated from a review of the cited documents, the metal containing product of the cited JP-776, is a <u>mixture</u> of metal compounds. In contrast, the present claims are directed to metal <u>compounds,</u> namely, compounds containing two or more metals, e.g., in the nature of hydrotalcite compounds.

Turning to the English translation of JP-776, it is seen from paragraph [0020] that, as suggested by the Examiner, the iron hydroxide gel used is prepared from iron chloride and sodium hydroxide. However, the stated understanding of Figures 1 and 2 does not appear to be correct. Thus, from the translation of paragraph [0024], Fig. 2 relates to aluminum hydroxide. Consequently, this figure is not deemed relevant to the claimed subject matter. Figure 1, does relate to iron hydroxide but does not show the compounds to be effective over the pH range of from 3 to 7, especially from 2 to 8. The upper curves in Fig. 1, relate to measurements at pH 2 and 3; the lower curves at higher pH. From these figures it is noted that the efficiency of the compound at higher pH's is very much lower than at low pH. Further clarification is seen from Fig. 3, as explained in paragraph [0024]. That is, Fig. 3 and

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paragraphs [0022] explain the calculations of phosphate binding capacity: using 500 ml of 10 mM phosphate solution (5 mmol), to which is added 1 gram of the iron compound. From Fig. 3, it is seen that at pH 2, 1.5 mmol of phosphate (left-hand scale) are absorbed, corresponding to 30%. Over the pH range 4 to 8, however, the best absorption is about 0.5 mmol, only about 10% absorption.

Accordingly, it is evident that this document merely confirms that iron hydroxide is an effective phosphate binder only at low pH, in particular, 2 to perhaps, 3. Over the pH range 4 to 8, iron hydroxide is about equivalent or only slightly better than aluminum hydroxide.

As such, one skilled in the art would not have been motivated to formulate a mixed metal compound containing iron with expectation of obtaining an efficient phosphate binder, particularly at pH levels above 3.

The disclosure of DE-878 does not overcome the deficiencies of JP-776.

First, the disclosure of DE-878 merely confirms the description on page 1, line 27 to page 2, line 5, that calcium compounds having poor solubility at pH 6-9, e.g., calcium carbonate, are known as phosphate binders, albeit with the drawbacks described. The same would be expected for the corresponding magnesium compounds. Given this knowledge in the state of the art, it is highly unlikely that the skilled practitioner would have been motivated to use the combination of the teachings of JP-776 with DE-878.

Furthermore, if one skilled in the art were to consider the combination, the expectation would still be that phosphate binding would diminish at high pH. Thus, taking the case of calcium carbonate (see, also the abstract of the family member EP 150 792B), it is shown in Fig. 8 of this application that phosphate binding capacity for magnesium hydroxide and calcium carbonate drops off at high pH.

Still further, of course, combining the disclosures of JP-776 and DE-878 would still result in only mixtures of e.g., iron hydroxide and calcium or magnesium carbonate, not a mixed metal compound as claimed herein. One skilled in the art would not be able to predict from the properties of the individual compounds, properties of a compound containing both metals. *In re Kerkhoven* does not apply to this situation.

In summary, the compounds of JP-776 are poor phosphate binders over the pH range of 4 to 8; the compounds of DE-878 also are deficient at high pH values; properties of individual compounds do not predict properties of mixed metal compounds; and the prior art

does not predict the properties of the presently claimed compounds nor render this invention obvious.

The references cited as showing the state of the art would not have suggested the presently claimed subject matter.

In view of the foregoing, the claims are now believed to be in form for allowance, and such action is hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned at the telephone number listed below.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached Appendix is captioned **"Version with markings to show changes made"**.

All objections and rejections having been addressed, it is respectfully submitted that the present application is in a condition for allowance and a Notice to that effect is earnestly solicited.

Respectfully submitted,

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Enclosure: Appendix

Date: January 22, 2002
Attorney Reference: 081935/0266300

APPENDIX: VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

The specification is changed as follows:

Page 1, lines 11-29:

In patients with kidney failure on haemodialysis (of whom there are 6,000,000 world wide), phosphate concentrations in the blood plasma can rise dramatically and such hyperphosphataemia can result in calcium phosphate deposition in soft tissue. Currently, the plasma phosphate levels are reduced by oral intake of inorganic and organic phosphate binders. The most common treatment in the UK is with [aluminium] aluminum hydroxide gel ("[Aludrox]ALUDROX®" at 4 g/day) which forms an insoluble [aluminium] aluminum phosphate. However, this results in further toxic complications due to Al accumulation, eg reduction in haemoglobin production, impairment in natural repair and production of bone and possible impairment of neurological/cognitive function. Improvements in phosphate binding capacity as compared with [aluminium] aluminum hydroxide gel have been achieved with other [aluminium] aluminum compounds such as microcrystalline [aluminium] aluminum oxide hydroxide (boehmite) and certain hydrotalcites have been made; Ookubo et al, Journal Pharmaceutical Sciences (November 1992), 81(11), 1139-1140. However, such compounds still result in an intolerable amount of [aluminium] aluminum accumulation in renal failure patients. It is also known to use calcium compounds having pool solubility at pH 6-9, eg calcium carbonate, hydroxide, oxide and/or sulphate in a medicinal form

Page 5, line 18: ●-● [Altacite] ALTACITE liquid washed

Page 5, line 24: ●-● [Altacite] ALTACITE liquid washed.

Page 6, line 1: ▼[Altacite] ALTACITE liquid unwashed

Page 9, line 22:

(6) [Altacite] ALTACITE, a hydrotalcite of the same formula as CT 100, commercially available from Roussell, in the form of an aqueous slurry

Page 10, fourth paragraph (lines 13-21):

Method 3 – Milk (250 ml), cornflakes (50 g), bread (2 slices) and [marmite] MARMITE (yeast extract) (5 g) were mixed in a stomacher for 30 minutes containing 0.01 M HCl (so as to simulate the conditions in the stomach). A 20 ml aliquot of food was removed and centrifuged. Phosphate was measured in the supernatant. Two grams of the phosphate binder compound was added to the bulk food slurry and mixed for a further 30 minutes. J an aliquot of food was taken and the phosphate measured in the supernatant following centrifugation. Further aliquots were taken after a further 30 and 90 minutes mixing.

Page 10, the last paragraph (lines 21-27):

In each of the above methods, for each of the compounds (1)-(4), where a dry powder was dosed as the phosphate binder, phosphate binding was measured for a given dosage measured after drying to constant weight at 40°C. Where a wet cake was dosed (or [Altacite] ALTALCITE (6) added), an amount equivalent to a given constant dry weight at 40°C was used. For known commercially available binders, a given weight of the material supplied

Page 13, the second paragraph (lines 4-7):

The compounds Mg:Fe 2:1 (1), Ca:Fe 3:1 (2) and CT100 (5) all bound up to 60-70% of the phosphate. Interestingly, the CT100 bound – 50% more phosphate at any weight than the [Altacite] ALTACITE (6) ,despite an identical molecular formulae.

Page 13, the sixth paragraph (lines 15-17):

At pH 7, the Mg:Fe 3:1 compound (2) was the best phosphate binder over the range of weights studied. The CT100 (5) bound at least twice as much phosphate than the [Altacite] ALTACITE (6) at any weight studied.

Page 16, the second full paragraph (lines 7-15):

The metals in the solutions/suspensions described in Table [1] 2 were precipitated at the same time by the addition of sodium hydroxide. A preparation was also made by precipitating the

calcium and iron separately with sodium hydroxide, the precipitates were then mixed. For this, $Fe_2(SO_4)_3$ (1 mole) and NaOH (6 moles) were mixed in 4 litres deionised H_2O. In a separate 4 litres of water, $CaSO_4$ (6 moles), NaOH (12 moles) and Na_2CO_3 (5 moles) were mixed. These two suspensions were then fed into the flask with an overflow at –2 litres and constantly mixed.

Page 39, first paragraph (lines 3-9):

Urine and serum [aluminium] <u>aluminum</u> concentrations were measured using graphite [furance]<u>furnace</u> atomic absorption spectroscopy. For the animals taking $Al(OH)_3$ or CT100, mean serum aluminum concentrations were not significantly higher than serum [aluminium] <u>aluminum</u> from control animals (Table 12). Surprisingly, animals treated with CTFeCa and CTFeMg showed the highest mean serum [aluminium] <u>aluminum</u> concentrations, both significantly higher [that] <u>than</u> animals treated with $Mg(OH)_2$, $Al(OH)_3$, $CaCO_3$ or controls.

<u>IN THE ABSTRACT OF THE DISCLOSURE</u>:

An Abstract is inserted.

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